DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Resea
1401 Rockville Pike
Rockville MD 20852-1448

WARNING LETTER

MAY 20 1997

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Inger Persson, M.Sc. Chem. Eng.
Responsible Head
Pharmacia & Upjohn AB
Lindhagensgatan 133
S-112 87 Stockholm, Sweden
U.S. License Number 1220

Dear Ms. Persson:

An inspection of Pharmacia & Upjohn AB facilities, located at S-112 87 Stockholm, Sweden; S-196 90 Kungsangen, Sweden; and S-645 41 Strangnas, Sweden, was conducted from March 3 through March 13, 1997. During the inspection, violations of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act and Title 21, Code of Federal Regulations, Part 211 and Parts 600-610 were documented, as follows:

1. Failure to establish and/or follow written testing programs designed to assess the stability characteristics of drug products [21 CFR 211.166] in that:

   a. the potency stability data for [redacted] Batch [redacted] does not support the product's [redacted] moth dating period.

   b. stability testing does not include analysis of [redacted] and [redacted] products.

   c. no [redacted] product was placed on the stability program in 1995.

   d. the potency for [redacted] Batch [redacted] and [redacted] was determined by [redacted] with [redacted] to obtain passing results.

2. Failure to have complete laboratory records including all data secured in the course of each test [21 CFR 211.194(a)] in that:

a. calculations of the initial test results obtained from the [redacted] potency assay for [redacted] Batch [redacted] and [redacted] are not maintained.

b. since January 1997, the production laboratory [redacted] of the [redacted] tank sample does not include recording the [redacted] reaction and morphology.

3. Failure to maintain complete laboratory records of any modification of an established method employed in testing including the reason for the modification [21 CFR 211.194(b)] in that there is no scientific justification for retesting out of specification results or discarding an assay result as an outlier obtained during the [redacted] potency assay.

4. Failure to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160(b)] in that:

a. the method for Quality Control test sampling of the two Water for Injection (WFI) systems is not representative of production use.

b. the validation study for the piping ending at [redacted] in the WFI system did not include data to justify the current sampling plan of [redacted] every [redacted] weeks.

5. Failure to calibrate instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program [21 CFR 211.160(b)(4)] in that:

a. the scale [redacted], used in the [redacted] test, was past due for calibration and had not been calibrated.

b. the function of the alarms for Freezers [redacted] used in the [redacted] area; Freezers [redacted] and [redacted] used for storage of [redacted]; and Refrigerator [redacted] in building [redacted] have not been checked.

6. Failure to thoroughly investigate any unexplained discrepancy or the failure of a batch to meet any of its specifications [21 CFR 211.192] in that:

a. there is no documentation indicating that the investigation of product failures extends to other batches of the same product and batches of other products that may have been associated with the specific failures of [redacted] Batch [redacted]

b. there is no documentation indicating an investigation was conducted regarding the initial out of specification test results for [redacted] Batch [redacted]

c. no investigation was conducted on batch [redacted] of [redacted] eluate which reached the bioburden limit of [redacted] CFU/mL

7. Failure of the quality control unit to approve or reject all procedures or specifications impacting on the identity, strength, quality, and purity of drug products [21 CFR 211.22(c)]. For example:

a. reuse and repacking of two chromatography columns used in [redacted] is performed using a procedure that is not approved by the quality control unit.

b. procedures are changed without the approval by the quality control unit in that:

i. the process development group approved manufacturing changes for pH adjustment of in-process [redacted] solutions and a change in the separator flow rate of [redacted] solutions without approval by the quality control unit.

ii. handwritten changes to standard operating procedure (SOP) QB-00-710-01 for animal care were not approved by the quality control unit.

8. Failure to conduct the appropriate laboratory testing to determine satisfactory conformance to final specifications for each batch of drug product, including identity and strength of each active ingredient prior to release [21 CFR 211.165] in that the release testing of [redacted] Batch [redacted] was performed with non-calibrated pyrogen test equipment.

9. Failure to provide drains of adequate size and with air break or other mechanical device to prevent back-siphonage [21 CFR 211.48(b)] in that during the washing and rinsing of the water bath [redacted] the water backed up from the sewer drain past the air break to the drain pipe.

10. Failure to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile and to assure that such procedures include validation of any sterilization processes [21 CFR 211.113(b)] in that:

a. WFI taps [redacted] and [redacted] in the [redacted] purification area are not sampled.

b. growth promotion testing was not conducted in the simulated fermentation studies performed to validate the sterilization procedures. Sterility of fermentation media is not measured for every batch.

11. Failure to maintain separate or defined areas or such control systems as necessary to prevent contamination or mixups [21 CFR 211.42(c)(10) and 600.11(a)] in that:

a. partially stoppered filled vials have not been shown to be maintained under Class 100 laminar flow conditions during transport to the lyophilizer.

b. the production lab laminar flow hood is not monitored each day during use for viable particulates.

12. Failure to establish and/or follow written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess and to assure that such procedures, including any changes, are drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by quality control [21 CFR 211.100]. For example:

a. there is no written procedure to describe rinsing the [redacted] ml bottles of [redacted] following [redacted] with cold WFI and ethanol before but not after removing the crimp seal.

b. there is no written procedure to describe how to interpret the virus reduction results from the [redacted] recording charts.

c. there is no written procedure to describe how to use WFI valves in a specific order to prevent dead legs from holding water at times when there is no demand for water.

d. the SOP QMB-05-05-01 for the calibration of the rabbit pyrogen temperature probes was not followed in that the stipulated temperatures for calibration were not used.

e. the SOP BB-4-04-1 for the care of laboratory rabbits was not followed in that new rabbits are not kept in a dedicated quarantine area [600.11(f)(2)] and the cages are not changed and washed weekly [600.11(f)(1)].

13. Failure to clean, maintain, and sanitize equipment and utensils at appropriate intervals to prevent malfunction or contamination that would alter the safety, identity, strength, quality, or purity of the drug product [21 CFR 211.67(a)] in that:

    a. the cleaning of shared equipment tanks in the sterile [redacted] product area is not validated.

    b. cleaned equipment in the [redacted] filling line is rinsed with city water and stored in a dry heat oven overnight prior to a final rinse with WFI.

    c. the cleaning method for water bath [redacted] is not validated.

14. Failure to maintain or follow written procedures for cleaning and maintenance of equipment including utensils, used in the manufacture, processing , packing, or holding of a drug product [21 CFR 211.67(b)] in that:

    a. the cleanliness of the water bath [redacted] was not checked before use as required by SOP KP-3450-01.

    b. there is no written procedure to describe the cleaning method used to clean water bath [redacted].

15. Failure to provide documentation of maintenance, cleaning, sanitizing, and inspection of equipment [21 CFR 211.67(c) and 600.12(a)] in that:

    a. the cleaning of water bath [redacted] and equipment tank [redacted] are not documented.

    b. records of autoclaving glassware used in the production laboratory are not maintained.

16. Failure to assure that the equipment used in the manufacture, processing, packing, or holding of a drug product is of appropriate design and of adequate size for its intended use and for its cleaning and maintenance [21 CFR 211.63] in that the validation of the WFI systems did not include determining if piping is installed to ensure it drains.

17. Failure to notify the Director, Center for Biologics Evaluation and Research (CBER), of proposed changes in location, equipment, responsible personnel, and manufacturing methods [21 CFR 601.12]. For example, the following changes were not reported to CBER:

    a. a [redacted] Computer System in the [redacted] area was installed and used.

b. the method of [redacted] for viral reduction of [redacted] was changed in 1990.

c. the WFI systems were renovated with the addition of process pipes.

We acknowledge receipt of your April 10, 1997, written response which addresses the inspectional observations on the Form FDA 483 issued at the close of the inspection and we will respond to your letter under separate cover.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deficiencies at your facilities. It is your responsibility as Responsible Head to assure that your facilities are in compliance with all the provisions of the Federal Food, Drug and Cosmetic Act and all applicable regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts.

Please notify this office in writing, within 15 working days of receipt of this letter, of any additional steps you have taken to correct the noted violations and to prevent their recurrence. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Corrective actions addressed in your April 10, 1997, letter may be referenced in your response to this letter, as appropriate. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions include seizure, license suspension, and/or revocation.

Your reply should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448, Attention: James C. Simmons, HFM-600.

Sincerely,

for James C. Simmons
Director, Office of Compliance
Center for Biologics Evaluation and Research

b. the method of [redacted] for viral reduction of [redacted] was changed in 1990.

c. the WFI systems were renovated with the addition of process pipes.

We acknowledge receipt of your April 10, 1997, written response which addresses the inspectional observations on the Form FDA 483 issued at the close of the inspection and we will respond to your letter under separate cover.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deficiencies at your facilities. It is your responsibility as Responsible Head to assure that your facilities are in compliance with all the provisions of the Federal Food, Drug and Cosmetic Act and all applicable regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts.

Please notify this office in writing, within 15 working days of receipt of this letter, of any additional steps you have taken to correct the noted violations and to prevent their recurrence. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Corrective actions addressed in your April 10, 1997, letter may be referenced in your response to this letter, as appropriate. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions include seizure, license suspension, and/or revocation.

Your reply should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448, Attention: James C. Simmons, HFM-600.

Sincerely,

for James C. Simmons
Director, Office of Compliance
Center for Biologics Evaluation and Research